Docket No.: 066654-0704 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Customer Number: 41552
Reed, John C.	:	Confirmation Number: 2174
Application No.: 10/030,497	:	Group Art Unit: 1643
Filed: June 27, 2002	:	Examiner: Sang, Hong

For: A METHOD FOR DETERMINING THE PROGNOSIS OF CANCER PATIENTS BY MEASURING LEVELS OF BAG EXPRESSION

PRE-APPEAL BRIEF REQUEST FOR REVIEW

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Commissioner for Patents
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I hereby certify that this correspondence is being electronically-transmitted to the United States Patent and Trademark Office on September 27, 2010.

/Ashley Campbell/

Ashley Campbell

Sir:

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request. A Notice of Appeal is submitted herewith. As set forth below, Applicant submits that clear error exists in the Examiner's rejection or that omissions of one or more elements needed for a *prima facie* case of obviousness have occurred.

Regarding Rejection Under 35 U.S.C. §103(a)

Claims 89, 90, 92, 95-101, 103, 106-110 and 114 stand rejected under 35 USC § 103(a), as allegedly being obvious over Froesch et al., Proceeding of the American Association for Cancer Research, Annual Meeting, 89:13 (March 1998), in view of Tang et al., Journal of Clinical Oncology, 17(6):1710-1719 (1999); Yawata et al., Oncogene, 16:2681-2686 (1998); and Sano et al. (U.S. Patent No. 5,665,539). Applicant maintains that (1) the Examiner has not articulated a credible rationale for combining the cited references, which are directed toward divergent cancer types; and (2) even if combined, the cited references provide no reasonable expectation of success for one of ordinary skill in the art to practice the claimed methods.

Briefly, claim 89, and all dependent claims thereof, are directed towards a method for determining the risk of tumor recurrence or spread in a patient suffering from prostate cancer by determining a cytosolic BAG-1 protein level in a cancerous prostate tissue sample from the patient and comparing the cytosolic BAG-1 protein level in the sample to a reference cytosolic BAG-1 protein level, wherein the

reference level correlates with an increased or decreased risk of tumor recurrence or spread. Claim 99, and all dependent claims thereof, are directed towards a method for determining a prognosis of survival in a patient suffering from prostate cancer by determining a cytosolic BAG-1 protein level in a cancerous prostate tissue sample from the patient and comparing the cytosolic BAG-1 protein level in the sample to a reference cytosolic BAG-1 protein level, wherein the reference level correlates with decreased or increased survival.

(1) Lack of a Credible Rational for Combining Cited References

The Examiner asserts that one of skill in the art would have been motivated to determine the prognostic function of both cytosolic and nuclear BAG-1 protein in prostate cancer based on the disclosure of Froesch et al., Tang et al. and Yawata et al. The Examiner asserts that the cited references disclose the following: Froesch et al. allegedly disclose BAG-1 protein (cytosolic BAG protein) is expressed in all 9/9 prostate cancer cell lines and 51/51 archival prostate tumor specimens (see Abstract); Tang et al. allegedly disclose that BAG-1 is overexpressed in the majority of invasive breast carcinomas, and by multivariate analysis, BAG-1 expression was significantly associated with shorter disease-free and overall survival (Abstract and Figures 3 and 4); and Yawata et al. allegedly disclose that overproduction of BAG-1 enhances cancer cell metastasis.

Applicant maintains that one of ordinary skill in the art would have had no motivation to combine the disclosure of Froesch et al. with the disclosures of Tang et al. and/or Yawata et al. to arrive at the claimed methods. At best, Froesch et al. disclose the expression of BAG-1L in prostate cancer (see Title and last sentence of abstract). At best, Tang et al. disclose that breast cancer patients whose tumors expressed nuclear BAG-1 tended to have shorter disease-free and overall survival (see page 1716, first column, lines 3-6, and Figure 4). At best, Yawata et al. disclose that overexpression of Bcl-2 or BAG-1 enhances peritoneal dissemination of human gastric MKN74 cells in nude mice (see Yawata at page 2682, left column, paragraph 1, lines 3-5; and page 2684 under the heading of *peritoneal dissemination of MKN74 transfectants*). One of skill in the art would have had no motivation to combine the disclosure of Froesch et al. regarding prostate cancer, with the disclosure of Tang et al. regarding breast cancer and the disclosure of Yawata et al. regarding gastric cancer, to achieve the claimed methods. Applicant submits that a person having ordinary skill in the art and having the capability of appreciating the complexity of scientific issues in cancer would most likely not combine the disclosures of such divergent cancer types to arrive at a method for determining the risk of tumor recurrence or spread in patients suffering from prostate cancer or determining a prognosis of survival of a prostate cancer patient, as claimed.

(2) No Expectation of Success – Teaching Away

The Examiner asserts that one of ordinary skill in the art would have had a reasonable expectation of success because Froesch et al. allegedly detected BAG-1 protein in all 9/9 prostate cancer cell lines and all 51/51 prostate tumor specimens, Tang et al. allegedly showed that in multivariate analysis, BAG-1 expression was significantly associated with shorter disease-free and overall survival, and Yawata et al. allegedly showed that overexpression of BAG-1 increased the metastatic potential of tumor cells *in vivo*.

Applicant maintains there is no motivation to combine the cited references, as articulated above. However, even if one skilled in the art were to have combined the teachings of the cited references, Applicant maintains that there would be no expectation of success because the disclosures of Froesch et al. and Tang et al. as evidenced by Takayama et al., when the references are viewed as a whole and combined, would lead one of ordinary skill in the art to conclude, at most, that the nuclear BAG-1 protein, i.e. BAG-1L, may be relevant to cancer prognosis. However, contrary to the claimed methods, the cited references actual teach away from a method for determining the risk of tumor or spread, or determining a prognosis of survival, by determining cytosolic BAG-1 protein expression. In order to clarify the different isoforms of BAG-1, briefly, BAG-1L is the longer protein isoform of the BAG-1 gene, as described in the specification on page 10, line 22 to page 11, line 9 and is known to one of skill in the art to be the isoform which contains a nuclear localization signal in the N-terminal region of the protein (see page 3121, Figure 3C of Takayama et al. Cancer Res. 58:3116-3131 (1998), which was cited by the Examiner in the Office Action of March 26, 2010, page 4). BAG-1L is also described in the specification to be the isoform found in the nuclear portion of the cell (see page 40, lines 7-11).

With regard to Froesch et al., Applicant maintains that, at best, the disclosure of Froesch et al. is directed towards BAG-1L (nuclear BAG-1 protein) expression in prostate cancer. Specifically, the title recites "BAG-1L protein is expressed in prostate cancers and enhances androgen receptor function." (emphasis added). Furthermore, the abstract discloses that BAG-1L, not BAG-1 (cytosolic BAG-1), co-immunopreciptated with androgen receptors (AR) from LNCaP cell lysates and markedly enhanced the ability of androgen receptors to trans-activate reporter gene plasmids in PC3 and other cell lines. The abstract concludes by reciting "These findings implicate BAG-1L as a novel regulator of AR function in prostate cancers." (emphasis added). Thus, the disclosure of Froesch et al. would, at most, lead one of ordinary skill in the art towards the nuclear BAG-1 protein, not the cytosolic BAG-1 protein, as most likely being associated with prostate cancer. Accordingly, Applicant maintains that Froesch et al. teach away from the claimed methods.

With regard to Tang et al., Applicant respectfully disagrees with the Examiner's characterization of Tang et al. Although Tang et al. may disclose that BAG-1 expression was significantly associated with shorter disease-free and overall survival using one type of analysis, when the disclosure of Tang et al. is taken as a whole, one of ordinary skill would most likely conclude there is little, if any, evidence that the expression pattern of BAG-1, i.e. nuclear BAG-1 protein vs. cytosolic BAG-1 protein, is associated with survival. Furthermore, if anything can be gleaned from the disclosure of Tang et al., it is that only the nuclear expression of BAG-1 protein, i.e. BAG-1L, might be correlated with survival (see Abstract). For example, Table 3 of Tang et al. (page 1714, second column; also reproduced in the Office Action Response filed July 13, 2010). shows that expression of BAG-1 and the stage of breast cancer were statistically correlated with shorter disease-free and overall survival using the multivariate analysis, whereas the expression pattern of BAG-1 was not statistically correlated with disease-free and overall survival ($P = .8544$ and $P = .7199$, respectively). Tang et al. also disclose that, when analyzed by univariate analysis, BAG-1 expression pattern did not correlate with either disease-free or overall survival (page 1713, first column, lines 5-6 from bottom). Still further, Tang et al. disclose that a Kaplan-Meier survival analysis showed that nuclear expression of BAG-1 only tended to be associated with a shorter disease free and overall survival, but "the differences did not reach statistical significance" (see page 1716, first column, lines 3-6, and Figure 4). Accordingly, Applicant maintains that Tang et al. teach away from the claimed methods.

The Examiner also asserts that the expression of cytosolic BAG-1 protein in prostate cancer was known, as evidenced by the disclosure of Takayama et al., *supra*. Specifically, the Examiner asserts that Takayama et al. disclose that BAG-1 (cytosolic) is expressed in 7 prostate cancer cell lines and is expressed at higher levels than BAG-1L (nuclear protein), referencing Table 2. Applicant respectfully disagrees with the Examiner's characterization of Takayama et al. Although Takayama et al. may disclose that seven prostate cancer cell lines express BAG-1, when the disclosure of Takayama et al. is taken as a whole, one of ordinary skill would most likely consider that the expression of nuclear BAG-1 protein (BAG-1L) is associated with the development of cancer, not cytosolic BAG-1 protein. For example, Takayama et al. on page 3130, right column, lines 16-22, characterize their results from Table 2: "An intriguing possibility is that BAG-1L, with its proclivity for nuclear targeting, may contribute to the regulation of nuclear hormone receptor function in these types of tumors, given the prominent role played by androgen receptor, ER, and glucocorticoid receptor in cancer of the prostate, breast and lymphoid organs, respectively." (emphasis added). Takayama et al. also summarize their results in the last sentence of the Abstract: "In contrast to normal tissues, which only rarely expressed BAG-1L, tumor cell lines

commonly contained BAG-1L protein, including most prostate, breast, and leukemia cell lines, suggesting that a change in BAG-1 mRNA translation frequently accompanies malignant transformation." (emphasis added). Thus, Takayama et al. disclose that the expression of nuclear BAG-1 protein accompanies malignant transformation. Accordingly, Applicant submits that Takayama et al. teach away from the claimed methods.

Regarding the disclosure of Sano et al., Applicant maintains that, at best, the reference discloses an immuno-PCR method. Thus, the disclosure of Sano et al. does not provide any reasonable expectation of success for one of skill in the art to practice the claimed methods, when combined with the disclosures of Froesch et al. and/or Tang et al. and/or Yawata et al.

In conclusion, the Examiner has not articulated a credible rationale for combining disclosures related to such disparate cancer types and, even if combined, the cited references do not provide a reasonable expectation of success in practicing a method wherein cytosolic BAG-1 protein levels are used to determine the risk of tumor recurrence or spread in a patient suffering from prostate cancer or to determine a prognosis of survival for a patient suffering from prostate cancer. Applicant submits that the rejection of claims 89, 90, 92, 95-101, 103, 106-110 and 114 under 35 USC § 103(a) as allegedly being obvious over Froesch et al., in view of Tang et al., Yawata et al. and Sano et al., is unsupported by the cited references and that clear error exists in the Examiner's rejection or the omission of one or more elements needed for a *prima facia* case of obviousness have occurred.

Respectfully submitted,

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